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A new predictive parameter for ischemic stroke: Inflammatory prognostic index-IPI

Comparison of combined inflammatory biomarkers

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Abstract
Aim: In stroke patients, there is a close relationship between the inflammatory response and poor prognosis. In this study, we aimed to compare the prognostic roles of NLR and CAR in ischemic stroke patients. In addition, we planned to formulate NLR with CRP and Albumin and to investigate the superiority of this parameter in predicting mortality and prognosis.
Material and Methods: Patients with the diagnosis of ischemic stroke in the tertiary intensive care units were retrospectively evaluated between August 2018 and October 2022. NIHSS, GCS, APACHE II scores, demographic data, comorbidities, treatment regimens, laboratory, and clinical variables were obtained from the hospital database. The IPI was calculated as C-reactive protein × NLR (neutrophil/ lymphocyte ratio)/serum albumin. CAR, NLR, PLR, and IPI were compared by ROC curves.
Results: Of the 660 patients in the study, NIHSS, APACHE II, CAR, NLR, PLR, and IPI constituted a risk for mortality in the multivariate analysis. AUC for CAR: 0.968, NLR: 0,980 PLR: 0,923, IPI: 0,984.
Discussion: Increases in NLR, PLR, CAR, and IPI correlate with mortality in ischemic stroke patients. The IPI parameter can be used safely and easily, like the other combined parameters such as CAR, NLR, and PLR.

Keywords
Ischemic Stroke, Mortality, NLR, PLR, CAR, IPI

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Introduction

Cerebrovascular disease (CVD), is a temporary or permanent damage to certain area of the brain as a result of bleeding or ischemia. On the other hand, an acute ischemic stroke is an impairment in cerebrovascular functions that occur suddenly due to impaired blood flow limited to a specific or global region. Symptoms last longer than 24 hours or can lead to sudden death without being identified for any reason other than a vascular event [1]. With the injury of the brain, disability and mortality become inevitable. Intravenous thrombolytic therapies, endovascular thrombectomy, anticoagulant, and antithrombotic therapies are various treatment methods.

There are many studies showing that neuroinflammation takes a great place in the worsening of ischemic stroke patients [2,3]. As a result of the blood flow pause, proinflammatory mediators, cytokines, and chemokines are released from many areas, including the activation of leukocytes and ischemic endothelium [4]. Because of these proinflammatory conditions, edema, and cellular damage, the clinical condition of patients become more and more exacerbated.

With the increase in the number of neutrophils, a simultaneous decrease in the number of lymphocytes is observed. Also, platelet counts increase with inflammation and play an important role in thrombogenesis [5]. Neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), MPV, and RDW have been studied previously to predict prognosis in stroke patients [6]. NLR and PLR were shown to have diagnostic and predictive importance in the prognosis of many different diseases [7].

The other two components of the inflammatory response are CRP and albumin. CRP increases in inflammatory conditions, trauma, and ischemic events. Contrarily, albumin decreases in malnutrition, trauma, malignancy, infection, and inflammation. These two parameters have been studied individually for years in inflammatory conditions. However, in recent studies, the CRP to albumin ratio (CAR) was found have higher prognostic and diagnostic value than these two parameters alone [8].

In this study, we planned to compare the prognostic roles of NLR and CAR values in ischemic stroke patients. In addition to these parameters, we planned to formulate NLR with CRP and albumin and investigate the superiority of this new parameter in predicting mortality and prognosis.

Material and Methods

Study design

We studied retrospectively in a single center. Nine hundred thirty-two patients who were followed up with the diagnosis of ischemic stroke in the tertiary intensive care units of Elazig Fethi Sekin City Hospital were evaluated between August 2018 and October 2022. Two hundred seventy-two of these patients were excluded from the study according to the exclusion criteria.

Inclusion and exclusion criteria

A total of 660 patients over the age of 18, who had any kind of ischemic stroke and were admitted within the first 72 hours of symptom onset, were included in the study. Patients 1) with acute infection, 2) with a diagnosis of sepsis, 3) with a diagnosis of malignancy, 4) with neurodegenerative disease, 5) with intracranial hemorrhage, 6) having undergone neurosurgery or other surgery in the last week, 7) with the known hematological disease, 8) with the known rheumatological disease, 9) receiving immunosuppressive therapy for any reason, 10) intoxication, 11) insufficient clinical and laboratory data, 12) previously diagnosed with ischemic stroke, were excluded from the study.

Data collection and definitions

The diagnosis of ischemic stroke was made by the definition of the World Health Organization and verified with Computed Tomography (CT) or Magnetic Resonance Imaging (MRI). Stroke severity during intensive care admission was determined by the National Institutes of Health Stroke Scale (NIHSS). The diagnosis and severity of ischemic stroke were determined by experienced neurologists working in our hospital who were not included in this study, and the data were obtained from the hospital's electronic system. Glasgow Coma Score (GCS) and APACHE II scores in the first 24 hours of admission to the intensive care unit, demographic data (age, gender), comorbidities (especially cardiovascular risk factors, eg, diabetes, hyperlipidemia, hypertension), treatment regimens, laboratory (CRP, Albumin, WBC, Platelet, Neutrophil, Lymphocyte) and clinical variables (mortality, number of intensive care unit stays) were obtained from the hospital database.

In the biochemistry laboratory of our hospital, albumin measurements were studied on AU-5800, CRP levels were determined by the nephelometric method on Image-800 protein Chemistry Analyzer (Beckman Coulter Inc., Minnesota, USA), and a complete blood count was analyzed on the DxH 800 device.

NLR is the ratio of the number of neutrophils to the number of lymphocytes.

PLR is the ratio of the number of platelets to the number of lymphocytes. CAR value was obtained by dividing the CRP value by the Albumin (gr/dl) value.

NLR: Neutrophil/Lymphocyte.

PLR: Platelet/Lymphocyte.

CAR: CRP/Albumin.

The IPI (Inflammatory Prognostic Index) value that we used in the data of our study was calculated using the formula: IPI: CRPxNLR/Albumin.

Ethics and approval

Informed consent of the patients for their antiischemic treatments was obtained during their stay in the intensive care unit, and anticoagulant, thrombolytic or mechanical thrombectomy treatment modalities were applied according to the protocol of our hospital.

Our study was approved by the ethics committee of Fırat University (2022-1209) and complies with the principles of the Declaration of Helsinki.

Statistical analysis

Analyzes were evaluated in 22 package programs of SPSS (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL). In the study, descriptive data were shown as n and % values in categorical data, and mean±standard deviation (Mean±SD) values in continuous data. Al logistic regression analysis was performed to calculate the mortality risk. Significant ones in the univariate analysis were included in the model for multivariate. Receiver operating characteristic (ROC) curves were drawn to measure the value of various parameters in predicting exitus. The statistical significance level in the analysis was accepted as $p<0.05$.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

The study included 660 patients who had undergone CVD and were hospitalized in the tertiary ICUs. The mean age of the patients was 77.0±10.5 years (min=30-max=98), 355 (53.8%) were females and 305 (46.2%) were males. Of the patients, 616 (93.3%) received anticoagulants and 44 (6.7%) received thrombolytics. While 181 (27.4%) of the patients were intubated, 181 (27.4%) died. Comorbidities were present in 652 (98.8%) patients, and 323 (49.5%) of those had HT, 318 (48.8%) had DM, 257 (39.4%) had CAD, 155 (23.8%) had HL, 47 (7.2%) had COPD, 42 (6.4%) had CHF, 14 (2.1%) had CRF, 12 (1.8%)) had Parkinson's disease and 12 (1.8%) had AF. The mean of the measurement data of the patients is shown in Table 1.

In the logistic regression analysis performed to calculate the risk of mortality, male gender, advanced age, and anticoagulant treatment created a risk for mortality according to the univariate analysis. In addition, GCS, NIHSS, APACHE II, increased number of ICU days, CAR, NLR, PLR, and IPI pose a risk for mortality. Significant ones in the univariate analysis were used in the multivariate analysis, and the increase in NIHSS, APACHE II, CAR, NLR, PLR, and IPI constituted a risk for mortality (Table 2). The optimal cut-off point for CAR was found to be 31,429 according to the ROC analysis for mortality, with sensitivity of 92,82 % and specificity of 95,41 %, and an area under the curve (AUC) of 0,968. The optimal cut-off point for NLR was found to be 7,723 according to the ROC analysis for mortality, with sensitivity of 97,79 % and specificity of 93,32 %, and an area under the curve (AUC) of 0,980. The optimal cut-off point for PLR was found to be 195,833 according to the ROC analysis for mortality, with sensitivity of 93,37 % and specificity of 83,51 %, and area under the curve (AUC) of 0,923. The optimal cut-off point for IPI was found to be 202,202 according to the ROC analysis for mortality, with sensitivity of 97,79 % and specificity

Table 1. All characteristics of the patients

		n	%
Age, Mean±SD		77,0±10,5	
Gender	Female	355	53,8
	Male	305	46,2
Treatment	Anticoagulant	616	93,3
	Thrombolytic	44	6,7
Entubation	Yes	181	27,4
	No	479	72,6
Mortality	Yes	181	27,4
	No	479	72,6
Presence of comorbidity	Yes	652	98,8
	No	8	1,2
Type of comorbidity	HT	323	49,5
	DM	318	48,8
	CAD	257	39,4
	HL	155	23,8
	COPD	47	7,2
	CHF	42	6,4
	CRF	14	2,1
	Parkinson's disease	12	1,8
	AF	12	1,8
GCS, Mean±SD		11,2±2,7	
NIHSS, Mean±SD		13,6±11,2	
APACHE II, Mean±SD		19,3±18,1	
Number of days in ICU, Mean±SD		12,7±18,8	
CRP, Mean±SD		78,6±102,7	
Albumin, Mean±SD		3,3±,6	
CAR, Mean±SD		30,5±44,1	
WBC, Mean±SD		10,3±4,3	
PLT, Mean±SD		246,5±103,1	
Neutrophil, Mean±SD		7,7±4,1	
Lymphocyte, Mean±SD		1,6±1,0	
NLR, Mean±SD		10,4±14,3	
PLR, Mean±SD		270,7±300,0	
IPI, Mean±SD		672,3±1358,3	

SD: Standard Deviation, GCS: Glasgow Coma Score, NIHSS: National Institutes of Health Stroke Scale, APACHE II: Acute Physiology and Chronic Health Evaluation, CRP: C-Reactive Protein, CAR: CRP to albumin Ratio, WBC: White Blood Cell, PLT: Platelet, NLR: Neutrophil to Lymphocyte Ratio, PLR: Platelet to Lymphocyte Ratio, IPI: Inflammatory Prognostic Index

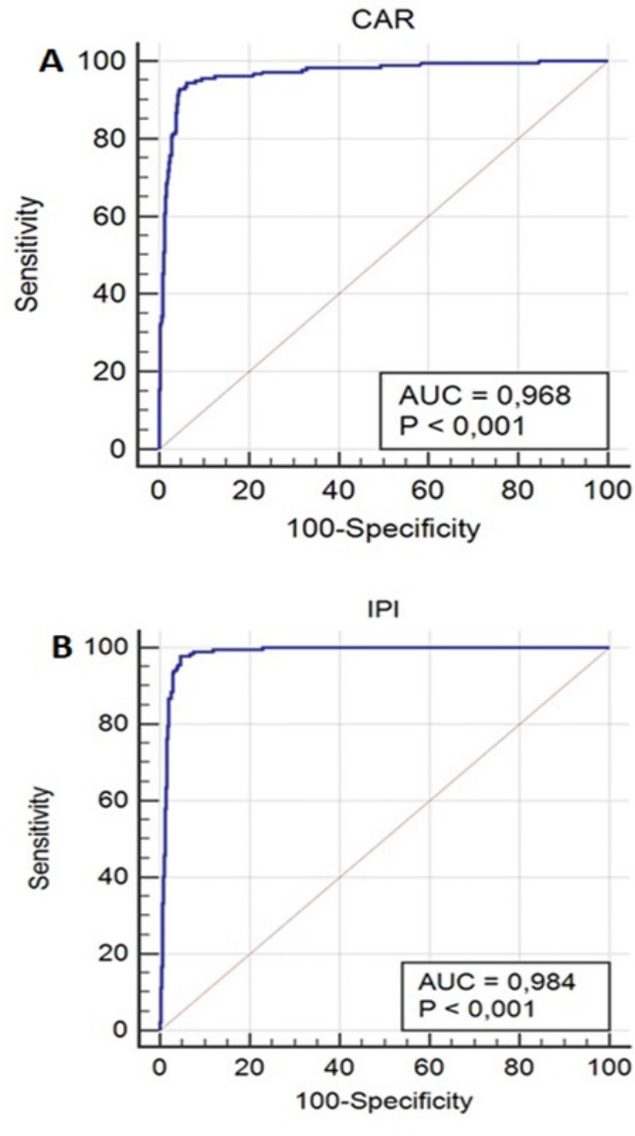

Figure 1.A- ROC curve for CAR-Mortality, B- ROC curve for IPI-Mortality, CAR: CRP to Albumin Ratio, IPI: Inflammatory Prognostic Index, AUC: Area Under Curve ROC: ROC: Receiver operating characteristic

Table 2. Logistic regression analysis of the presence of mortality

	Univariate				Multivariate			
	B	p	OR	%95 CI	B	p	OR	%95 CI
Gender (ref=female)	0,408	0,02	1,505	1,067-2,121	0,013	0,985	1,013	,248-4,137
Age	0,043	<0,001	1,044	1,024-1,063	0,069	0,095	1,072	,988-1,163
Treatment (ref=thrombolytic)	0,922	0,04	2,513	1,044-6,051	2,279	0,107	9,765	,611-156,014
GCS	-1,362	<0,001	0,256	,202-,325	0,599	0,117	1,82	,860-3,850
NIHSS	0,446	<0,001	1,562	1,430-1,705	0,296	0,006	1,344	1,089-1,660
APACHE II	0,188	<0,001	1,207	1,170-1,244	0,097	0,003	1,102	1,034-1,175
Number of ICU days	0,016	0,001	1,016	1,007-1,025	-0,016	0,213	0,984	,959-1,009
CAR	0,089	<0,001	1,093	1,078-1,108	0,106	<0,001	1,112	1,075-1,151
NLR	284	<0,001	1,329	1,271-1,389	0,255	<0,001	1,29	1,163-1,431
PLR	0,007	<0,001	1,007	1,004-1,008	0,003	0,006	1,003	1,001-1,015
IPI	0,003	<0,001	1,003	1,003-1,004	0,003	<0,001	1,003	1,002-1,004

B: Unstandardised regression, OR: Odds Ratio, CI: Confidence Interval, GCS: Glasgow Coma Score, NIHSS: National Institutes of Health Stroke Scale, APACHE II: Acute Physiology and Chronic Health Evaluation, ICU: Intensive Care Unit, CAR: CRP to albumin Ratio, NLR: Neutrophil to Lymphocyte Ratio, PLR: Platelet to Lymphocyte Ratio, IPI: Inflammatory Prognostic Index

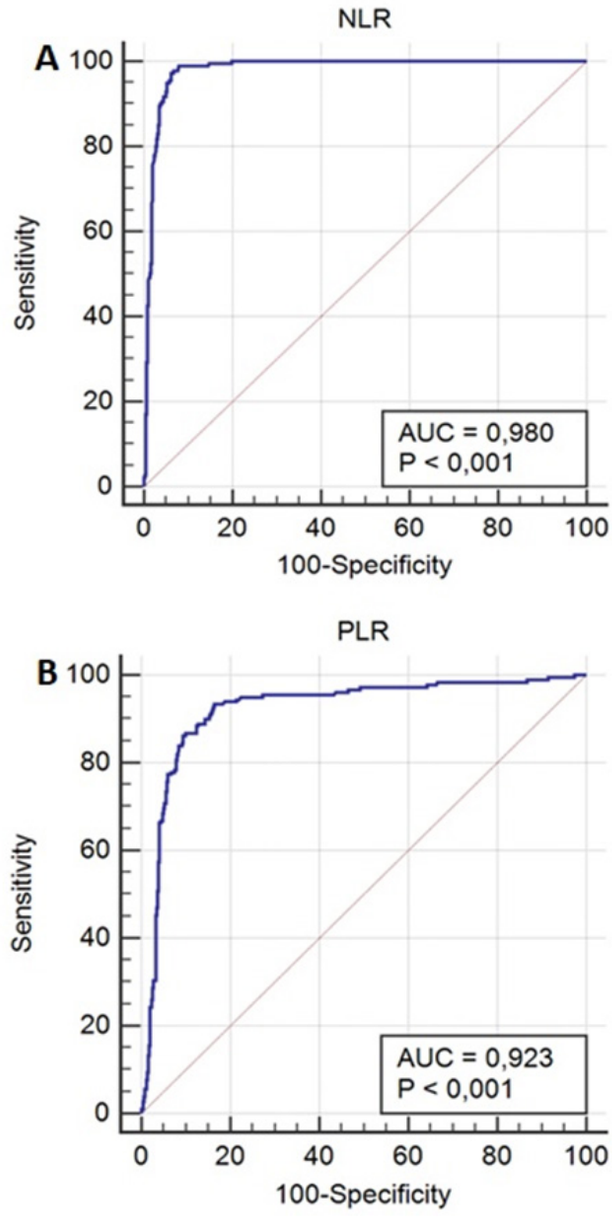

Figure 2.A- ROC curve for NLR-Mortality, B-ROC curve for PLR-Mortality, NLR: Neutrophil to Lymphocyte Ratio, PLR: Platelet to Lymphocyte Ratio, AUC: Area Under the Curve, ROC: Receiver operating characteristic

Table 3. ROC analysis results of various values according to exitus status

	CAR	NLR	PLR	IPI
Cut-off point	>31,429	>7,273	>195,833	>202,202
Sensitivity	92,82%	97,79%	93,37%	97,79%
Specificity	95,41%	93,32%	83,51%	95,41%
Positive predictive value	88,40%	84,70%	68,10%	88,90%
Negative predictive value	97,20%	99,10%	97,10%	99,10%
AUC	0,968	0,98	0,923	0,984
AUC %95 CI	0,952-0,980	0,967-0,990	0,900-0,842	0,974-0,992
AUC p-value	<0,001	<0,001	<0,001	<0,001

of 95,41 %, and an area under the curve (AUC) of 0,984 (Table 3, Figure 1A-B, 2A-B).

Discussion

Although the diagnosis and availability of advanced treatment methods are developing day by day, stroke still remains a major cause of mortality and long-term morbidity. Mortality still varies between 20-30 % [9].

Mainly neutrophils, white blood cells, platelets, and mediators accumulate in the ischemic area [13-15]. With the secretion of various oxygen radicals, cytokines, and matrix metalloproteinase-9 (MMP-9) from neutrophils, damage to the blood-brain barrier occurs. Increase in cellular damage, edema, and bleeding are observed [10]. These factors trigger the exacerbation of brain damage and worsen the clinical situation [11]. The stress state that occurs with the increase of inflammation creates an immunosuppressive environment and apoptosis of lymphocytes is observed [12]. This causes the neutrophil-lymphocyte balance to deteriorate. It is known that there is an increase in platelet count and thrombogenesis in case of inflammation. Platelet-lymphocyte ratio (PLR) and the effect of this ratio on prognosis in various diseases have been included in various studies [13]. Altıntaş et al associated high PLR value with insufficient recanalization, increased infarct area, and poor prognosis in ischemic stroke patients. When we looked at the relationship of PLR with mortality, we found 93.37% sensitivity and 83.51% specificity at a cut-off value of

195.83 (CI: 0.900-0.842). AUC was 0,923. These values show us that PLR can be used to predict prognosis in ischemic stroke-related inflammation [14].

We think that if the prognosis of ischemic stroke can be predicted with biomarkers, mortality and disability can be prevented. To date, many studies have shown the increase of inflammation in ischemic brain injury and its adverse consequences. However, it is not yet clear which of the measured parameters is more prognostic. We used parameters such as CAR, NLR, and PLR, which have been studied before, and compared their advantages in predicting prognosis. We investigated the superiority of the inflammatory prognostic index (IPI), which is found by formulating NLR, CRP, and albumin. Instead of using these markers separately, we thought that the combination might be more predictive of the prognosis of the disease. The primary endpoint was patients' mortality. According to our data, more than 80% of the patients had cardiovascular risk factors such as hypertension, hyperlipidemia, diabetes mellitus, and their mean age was 77 years. There was a correlation between age and mortality in the univariate regression analysis, but we found that it did not significantly increase mortality in the multivariate regression analysis. In both univariate and multivariate regression analyzes, we found that high NIHSS and APACHE II scores, CAR, NLR, PLR, and IPI values are independent risk factors for increased mortality.

NLR has been studied in many areas such as malignant diseases, immune diseases, and cardiovascular diseases, and it has been found valuable in predicting prognosis in most studies [8,15]. Studies showed the increased NLR as a reason of the formation and fragility of atherosclerotic plaque [16]. The

fragility of this plaque also causes it to rupture and cerebrovascular stenosis, ulceration, and new inflammation area occurs. In addition, NLR has been shown as an independent factor of the severity of ischemia, hemorrhagic complications, and poor prognosis [17-20]. In our study, when we look at the relationship between NLR and mortality according to Receiver Operating Characteristics (ROC) analysis, the cut-off value was 7.72 (CI: 0.967-0.990). We found an increase in mortality when the NLR was >7.72. Sensitivity at this point is 97.79%; specificity is 93.32% and AUC is 0.98. With these values, we can say that NLR is an important prognostic factor in ischemic stroke.

CRP is synthesized from hepatocytes, especially induced by interleukin-6 (IL-6). Compared to other proinflammatory cytokines, it is faster, easier, and cheaper to study, which is its advantage. There are studies indicating that the increase in CRP is also correlated with tissue damage and mortality in cerebral ischemia [21]. Albumin is a negative acute phase reactant synthesized from hepatocytes and decreased in case of inflammation. In inflammatory conditions, due to increased vascular permeability, blood albumin level is decreased. In recent studies, it has been shown that examining these two parameters separately has less prognostic importance than the CAR value [8,22]. Bender et al. showed that the CAR value of patients with intracranial hemorrhage predicted in-hospital mortality. We found the optimal cut-off value for CAR to be 31.43 (CI: 0.952-0.980) with 92.82% sensitivity, 95.41% specificity, and 0.968 AUC [23]. We can say that CAR is one of the parameters that can be easily and safely used in predicting mortality, although its specificity, sensitivity, and success are slightly lower when compared to NLR.

Inflammation and its high correlation with mortality of stroke patients require early prediction of prognosis and taking preventive measures. For this reason, easy and fast availability, low cost, and reliable parameters are needed. Combined parameters such as NLR, PLR, and CAR can be obtained quickly from whole blood count and biochemical parameters and have prognostic importance in inflammation. Routine monitoring in clinical practice also provides convenience. IPI has been studied very recently. It has been used in several malignancy studies before and has been found to be associated with mortality [24]. We studied IPI in cerebral ischemia with intense inflammation in the early period. The optimal cut-off point was 202.2 (CI: 0.972-0.992) in our study. At this point, we can say that it is more successful than other parameters in predicting the prognosis with 97.8% sensitivity, 95.41% specificity, and 0.984 AUC value. Like other parameters, IPI can be checked with routine blood tests. It is also important that it is easy, cheap, and quickly available. The fact that it is superior to CAR, NLR, and PLR suggests that it can be used in many areas. Cut-off values in this study were different from other studies. This may be due to the variety of study groups and unitary differences.

Conclusion

As the inflammatory process is a remarkable factor in ischemic stroke prognosis, we recommend determining the severity of inflammation to predict the severity and prognosis of the disease in these patients. Thus, we think that both mortality and disability can be reduced by making the necessary preventive and protective treatment and care plans. For all of these reasons, we argue that the IPI parameter can be used safely, apart from the combined parameters such as CAR, NLR, and PLR.

Limitations

The most important limitation is that the study was retrospective and single-center. However, we planned to conduct this study prospectively with a larger patient group. Since the study is retrospective, the subtypes of stroke could not be categorized and the Modified Rankin Scales of the patients could not be accessed from our hospital database. Although inflammation is more intense in the first 72 hours of symptom onset, NLR, PLR, CAR, and IPI values will be studied dynamically in the prospective study.

Learning points

- Ischemic stroke is an important cause of mortality and morbidity in intensive care units.
- In the early stages of ischemia, inflammation plays an important role.
- Inflammation is important in the prognosis of ischemic stroke patients.
- CAR, NLR, PLR, and IPI are important prognostic factors for ischemic stroke patients.

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Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some

of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflict of interest
The authors declare no conflict of interest.

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